Remarks

Status Of Claims

Claims 19-24, 26-55 and 61 - 63 are pending.

Claims 19-24, 26-55 and 61 - 63 stand rejected.

Amendments to the Specification

Applicants have amended the specification to include a statement regarding federally sponsored research or development. The amendment does not introduce new matter.

Amendment to the Claims

Applicants have amended Claim 19 to recite "culturing" in the first step, as recited in Claim 1 as filed. It is clear from the specification that the term "culturing" is used interchangeably with "incubating", and that contacting the sample with the antigen is required. The amendment does not introduce new matter.

Formal Drawings

Applicants submit concurrent herewith, as a separate paper, formal drawings in response to PTO Form 948, mailed 3/27/00. Although the originally filed informal drawings were in color, color is not needed for clarity, and Applicants are submitting formal drawings in black and white.

The Rejection of Claims 19-24, 26-33, 40, 43, 45, 47, 49-55, and 61-63 under the written description requirement of 35 U.S.C. §112, first paragraph

Claims 19-24, 26-33, 40, 43, 45, 47, 49-55, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, for reasons of record, i.e., on the ground that the specification provides insufficient written description of the generic claim reciting the use of an inhibitor of cytokine secretion. Examiner, noting the large number of compounds that potentially could be encompassed by the term "inhibitor of cytokine secretion",

suggested that the claimed genus has not been adequately described. Applicants traverse for the reasons set forth below.

Applicants maintain that the rejection is improper and contradicts the precedent of the case law cited herein. The description need only describe in detail that which is new or not conventional, and this aspect of the claimed method is old in the art. In particular, where claims are drawn to the use of known compounds, as they are in the present case, and are *not* drawn to either novel compounds per se or methods using novel compounds, the applicant is not required to discover all the compounds from this class that would be useable in the methods. Applicants discuss these two points more fully, below.

1) The genus "inhibitors of cytokine secretion", and the use thereof, is old in the art

The claims are drawn to novel methods for detecting antigen-specific T cells by detecting intracellular cytokines following stimulation by contact with a nominal antigen; an inhibitor of cytokine secretion is used to allow intracellular cytokines to accumulate. A critical aspect of the claimed methods that distinguishes them over previous methods is the combination of (1) selective activation of antigen-specific T cells using a nominal antigen, rather than general activation of T cells in a non-specific manner, with (2) detection of intracellular cytokines that selectively detect only the desired subpopulation of antigen-activated, antigen-specific T cells. In contrast, the use of an inhibitor of cytokine secretion to allow intracellular cytokines to accumulate in activated T cells was old in the art at the time of the present invention.

The art of record describes the detection of intracellular cytokines following the general activation of T cells in a non-specific manner. As in the claimed methods, an inhibitor of cytokine secretion is used to allow intracellular cytokines to accumulate. Both inhibitors of cytokine secretion and their use to allow cytokines to accumulate in an activated T cell were old in the art. Thus, the class of compounds with the property of being a inhibitor of cytokine secretion suitable for use in the claimed methods was known in the art. The description need only describe in detail that which is new or not conventional (*Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94 (Fed. Cir. 1986)). The rejection is improper in that it is based on an improper requirement to describe in great detail a class of compounds which is old in the art.

2) Applicants are not required to discover all the compounds within the genus that would be useable in the methods

As discussed above, the claimed methods incorporate a step wherein a compound from a known class of compounds is used in a known manner to achieve a known result. The courts, in clarifying the written description requirement, have distinguished claims drawn to novel combinations or uses of known compounds from claims drawn to classes of new compounds per se or claims drawn to processes using those new compounds.

For example, in *In re Fuetterer*, 138 USPQ 217 (CCPA 1963), claims drawn to a rubber stock composition useful in producing tire treads included a recitation of "an inorganic salt capable" of maintaining an homogeneous distribution of another component in the composition. The disclosure listed the function desired and four members of the class having that function. The claims had been rejected by the examiner as being overly broad ("'inorganic salt" reads on literally thousands of materials, many of which would not be operative for applicant's purpose'. Ibid at 220). The board agreed, noting that rejection was based on "the inordinate breadth of the claimed salts when it is not apparent from the disclosure of only four salts what other salts would be suitable to serve the function asserted and required by the claims" (Ibid at 220, 221). However, the Court overturned the rejection and found the written description requirement to be satisfied:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

Ibid at 138 USPQ at 223 (emphasis added). The reasoning in *In re Fuetterer* is consistent with the reasoning in *Hybritech v. Monoclonal Antibodies* (cited above) that Applicants need not describe in detail elements of the invention that are old in the art.

Analogous to *In re Fuetterer*, the present claims are to a method using a known class of compounds that are useful as inhibitors of cytokine secretion, not the discovery that certain compounds act as inhibitors of cytokine secretion. Following the reasoning of the Court, Applicants do not have to discover which of all the potential inhibitors of cytokine secretion will function properly in methods. Furthermore, if others in the future discover another suitable inhibitor of cytokine secretion, the present claims should not be so restricted that they can be avoided merely by using some inhibitor of cytokine secretion not described in the specification.

In summary, Applicants believe that the rejection represented an improper requirement that specification describe in detail elements of the invention that are old in the art. Applicants maintain that the description in the specification is sufficient to reasonably convey to one of skill in the art that Applicants conceived of methods using the previously known class of compounds, "an inhibitor of cytokine secretion". For these reasons and in view of the case law discussed above, Applicants submit that the specification fully meets the written description requirement. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 19-24, 26-33, 40, 43, 45, 47, 49-55, and 61-63 under the written description requirement of 35 U.S.C. §112, first paragraph.

The Rejection of Claims 19-24, 26-55, and 61-63 under the enablement requirement of 35 U.S.C. §112, first paragraph

Claims 19-24, 26-55, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement (Paper 40, §8). Applicants traverse for the reasons set forth below in addition to the reasons of record.

Applicants note that present rejection essentially is a restatement of the enablement rejections discussed extensively in previous Office actions. After extensive submissions from Applicants, included declarations from Dr. Prussin, the enablement rejections were fully withdrawn in the Office action dated August 31, 2001 (Paper 28). Examiner has restated the enablement rejection, apparently based on an assumption that

success of the claimed invention is highly unexpected and, therefore, only the exemplified preferred embodiment is enabled by the specification:

> As the percentage of T cells that respond to any particular antigen is very small, the ability to detect said response is highly dependent of several critical factors (see particularly Example 4 of the specification). In addition, Applicant has argued that said detection ability is highly unexpected (see declarations of Drs. Altman and Prussin), thus, said detection ability must be considered to be absolutely dependent of [sic] the limitations set forth in the specification

Paper 40, page 5, first paragraph (citing *In re Mayhew*). Applicants respectfully point out that the premise on which the rejection is based is not valid, as the unexpectedness of the claimed invention is based on the understanding and expectation of one skill in the art at the time of the invention, without benefit of Applicants' teaching, rather than on the enablement provided in the specification.

Applicants previously provided, in response to a rejection under 35 U.S.C. §103, arguments based on the understanding and expectation of one of ordinary skill at the time of the invention. In particular, the Second Declaration by John D. Altman ("The Altman 2nd Dec", cited in Applicants' previous response) provides expert testimony that one of skill in the art at the time of the invention would have expected that the number of antigen-specific T cells that express intracellular cytokines would be too small to detect using flow cytometric methods (see §§19-22). However, the Altman 2nd Dec further points out that the unexpected success of Applicants' methods contributed to a fundamental revision in the belief of one of skill in the art as to the frequency of memory T cells (see the Altman 2nd Dec, §22). The success of Applicants' methods taught that the frequency of memory T cells was much higher than previously believed (see also the specification, paragraph spanning pages 10 and 11).

Enablement of the invention must be considered in view of the teachings of the specification, not on the expectation of one of skill in the art at the time of the invention, who did not have the benefit of Applicants' teachings. The specification as a whole does not teach that the methods are dependent on the exact protocols described in the examples. In fact, the specification clearly teaches that "The examples illustrate certain preferred embodiments of the invention but are not intended to be illustrative of all embodiments" (page 13, lines 16-17; see also page 18, lines 13-14).

Applicants wish to point out that the facts in the present case are distinguished from those in *In re Mayhew*, cited by Examiner as precedence for the rejection. In *In re Mayhew*, the specification contained multiple teachings that the invention was dependent on a specific feature (a cooling zone, specifically located), and this feature was omitted entirely in the broadest claim. The teachings of the specification indicated that the best mode (i.e., with a cooling zone present) was, in fact, the only mode supported. This is in contrast to the facts of the present invention wherein the specification describes the invention more broadly, in addition to providing detailed descriptions of preferred examples. Furthermore, arguments and evidence of record, provided in previous responses, show that the invention can be carried out more broadly without undue experimentation, as taught in the specification. Thus, the reasoning of the Court in *In re Mayhew* is not applicable to the facts of the present case.

For the reasons discussed above, Applicant urge that there is no basis for restating the enablement rejections which were overcome previously. Applicants provide additional comments on particular points raised in the restated rejection, below.

Culturing

Applicants have amended Claim 19 to recite "culturing" the sample with an antigen. It is clear from the specification that the term "culturing" is used interchangeably with "incubating" the sample with the antigen (e.g., page 6, line 7 and page 14, line 3). Applicants believe that this amendment renders moot Examiner's concerns over the wording of Claim 19.

Costimulation

Examiner stated, without support, that "it is well-established that antigen stimulation in the absence of costimulation (....) will result in anergy (not activation)" (Paper 40, page 5). Applicants' respectfully point out that endogenous costimulation inherently is provided by antigen presenting cells (APC) in the sample, making the addition of an exogenous costimulant unnecessary. The addition of an exogenous costimulant (as recited in Claim 20) is carried out to maximize the response, not to enable the method (see Example 4, page 16, lines 16-18; see also Page 5, lines 4-13).

Example 4

The examples illustrate certain preferred embodiments of the invention but are not intended to be illustrative of all embodiments (specification, page 13, lines 16-17). In particular, Example 4 provides teaching of a preferred embodiment which maximizes response and accuracy of detection, including the use of slant tubes to maximize response, gating using CD69, the timing of the introduction of Brefeldin A to maximize response, and number of events collected to achieve detection accuracy. These teachings are clearly directed to a preferred embodiments and do not represent the only supported embodiment.

Inhibitor of cytokine secretion

Examiner stated that the specification and the post-filing art disclose/teach that the inclusion of an inhibitor of cytokine secretion is essential (Paper 40, page 5). However, the inclusion of such an inhibitor is a limitation of all of the claims. As discussed above with respect to written description, the use of an inhibitor of cytokine secretion to allow accumulation of cytokines within activated T cells was known in the art. One of skill in the art, following the teaching of the specification and without undue experimentation, could carry out the claimed methods using a known inhibitor of cytokine secretion.

Examiner cited O'Neil-Andersen and Lawrence ("O'Neil-Andersen") as teaching that different inhibitors of cytokine secretion, Brefeldin A (BFA) and monensin (MN), would yield different results. O'Neil-Andersen describes the use of BFA and MN as inhibitors of cytokine secretion in flow-cytometric assays for the detection of intracellular cytokines following general activation of T cells in a non-specific manner (using PMA and ION). The methods are equivalent to those described in the art of record. O'Neil-Andersen describes successful results using both BFA and MN, which confirms what was known in the art at the time of filing, that BFA and MN are useful as inhibitors of cytokine secretion to allow intracellular cytokines to accumulate in activated T cells. While the focus of O'Neil-Andersen's study was on elucidating performance differences, the performance differences reported were differences between two successful methods,

and do not suggest that either is not a working embodiment of the methods. It is not a requirement that all embodiments of an invention work equivalently to the preferred embodiment.

In summary, Applicant urge that there is no basis for restating the enablement rejections which were overcome previously. Furthermore, it would be improper to restrict the claimed methods to the specific preferred embodiment described in Example 4. For these reasons, Applicants respectfully request reconsideration and withdrawl of the rejection of Claims 19-24, 26-55, and 61-63 under the enablement requirement of 35 U.S.C. §112, first paragraph.

The Provisional Obviousnes-type Double Patenting Rejection

Claims 19-24, 26-55, and 61-63 stand provisionally rejected over Claims 1-37 and 39-40 of copending Application No. 09/526,253. As this is a provisional rejection, Applicants will respond to this rejection at such time as claims are found allowable in the '253 application.

Conclusion

Applicants respectfully submit that all rejections have been traversed or rebutted and that the application is in condition for allowance. Applicants respectfully request that all pending claims be allowed.

Respectfully submitted,

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Date

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Version With Markings To Show Changes Made

In the Claims:

19. (amended four times) A method of detecting T lymphocytes that are specific for a nominal antigen, comprising:

[contacting]culturing a sample containing peripheral blood mononuclear cells with a nominal antigen;

adding to said sample an inhibitor of cytokine secretion;

permeabilizing said cells;

adding to said sample at least one cytokine-specific antibody and at least one T lymphocyte subset-defining antibody; and then

flow cytometrically detecting the intracellular binding of said cytokine-specific antibody by cells in the defined T lymphocyte subset.